UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE NUVARING® PRODUCTS LIABILITY LITIGATION	))))	**4:08-MD-1964 RWS** **MDL No. 1964**

This Document Relates to:

MARIANNE PRATHER,	**4:08-cv-0558-RWS**

Plaintiff,

v.

ORGANON USA, INC., *et al.*

Defendants.

PLAINTIFF'S RESPONSE IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE EXPERT TESTIMONY OF JOHN RICHART, M.D.

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I. INTRODUCTION

Defendants' claim that Dr. Richart's medical causation opinions relating to NuvaRing® being the cause of Mrs. Prather's pulmonary embolism constitute a "logical fallacy." *See* Defendants' Motion To Exclude John Richart, M.D. ("Defs' Motion"), Doc No. 28, at 1. Defendants' argument not only lacks support, but is premised on the mischaracterization that the sole basis of Dr. Richart's opinion, which is referred to as a 'one-patient cross-over trial'[1], is a "made-up methodology". *Id.* at 5. *This is simply not the case.* In reaching his opinions, Dr. Richart did not limit his analysis to considering only Plaintiff's past and current contraceptive use, but instead considered an extensive amount of data, medical and scientific literature, medical information and risk factors pertinent to Plaintiff's case in utilizing a proper differential diagnosis.

Dr. Richart's medical causation opinions are based on a proper 'differential diagnosis', which is a technique utilized by medical experts whereby the cause of a medical condition is ascertained by eliminating the likely causes until the most probable cause is isolated. *See Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1208 (8th Cir. 2000) (citing *Westberry v. Gislaved Gummi AB*, 78 F.3d 257, 262-63 (4th Cir. 1999)). It is well-established in the Eighth Circuit that a medical causation opinion based on a proper differential diagnosis is sufficiently reliable to satisfy *Daubert* and Rule 702. *See e.g., Turner*, 229 F.3d at 1208; *Bland v. Verizon Wireless, (VAW) L.L.C.*, 538 F.3d 893, 897 (8th Cir. 2008); *Campbell v. Big Lots Stores, Inc.*, No. 4:09-cv-1268, 2011 U.S. Dist. LEXIS 59099, *6 (E.D. Mo. June 2, 2011).

[1] The fact that Dr. Richart referred to his approach as a "one-patient cross-over trial" within his Report is irrelevant. The bottom line is that Dr. Richart reviewed sufficient evidence and systematically 'ruled in' potential causes and 'ruled out' potential causes, so that his medical causation opinions are based on a proper differential diagnosis, and are thus sufficiently reliable to satisfy the requirements of *Daubert* and Rule 702.

It is clear that Dr. Richart thoroughly reviewed an extensive amount of materials and data in utilizing the technique of differential diagnosis to form the basis of his medical causation opinions. *See* Declaration of Dr. John M. Richart, at ¶9, attached hereto as Exhibit 1. As explained by Dr. Richart, he systematically ruled in plausible causes and ruled out possible causes in opining, within a reasonable degree of medical certainty, that Mrs. Prather's use of NuvaRing® was the most probable cause of her venous thromboembolism ("VTE"). *See* Exhibit 1 at ¶¶6-13. Because Dr. Richart reviewed sufficient evidence and systematically 'ruled in' potential causes and 'ruled out' potential causes, Dr. Richart's causation opinions are based on a proper differential diagnosis and are thus sufficiently reliable to satisfy the requirements of *Daubert* and Rule 702.

Importantly, Dr. Richart is Plaintiff's sole expert witness testifying as to medical causation. Thus, Dr. Richart's medical causation testimony is clearly necessary in order to assist the jury due to the fact that his causation opinions encompass medical information and observations not obvious to a layperson. Defendants' criticism of Dr. Richart's opinions (particularly through the use of selected portions of deposition testimony, often taken out of context) is a matter for cross-examination and does not provide any basis for excluding him from testifying as an expert witness at trial.

It is evident that Defendants' challenges amount to nothing more than an attempt to divert the Court's attention away from the fact that Dr. Richart is a well-qualified expert witness who has utilized reliable methodology in the formation of his medical causation opinions that will greatly assist the jury in understanding the case. For these and further reasons as discussed herewith, Defendants' Motion to Exclude the Testimony of Dr. John Richart should be denied.

II. FACTUAL BACKGROUND

The NuvaRing® is an ethylene vinyl acetate copolymer plastic ring that delivers two active components - etonogestrel (a third generation progestin) and ethinyl estradiol (the estrogen component). *See* Case-Specific Expert Report for Marianne Prather prepared by Dr. John M. Richart, at 10, attached hereto as Exhibit 2. Plaintiff was provided with a prescription of NuvaRing® on August 13, 2003 and began using NuvaRing® at the end of August 2003. *Id.* Plaintiff then began her second cycle of NuvaRing® in late September 2003. *Id.*

At the end of September 2003 Plaintiff began to experience leg discomfort, with increased pain in her left leg, and shortness of breath.[2] *Id.* at 10. On October 4, 2003, Plaintiff visited the emergency room at St. Joseph's Health Center. *Id.*; Deposition of Dr. John Richart, Nov. 18, 2011, at 190:21-191:2, 193:7-10, attached hereto as Exhibit 3. In the emergency room a CT scan was performed, which revealed multiple pulmonary emboli – in particular a large filling defect at the distal aspect of the right main pulmonary artery extending into the intermediate pulmonary artery and at least two lower lobe segments. *See* Exhibit 2 at 10. Plaintiff was immediately treated with anticoagulation therapy,[3] including Heparin, and was hospitalized for four days. *Id.* at 10-11. On October 8, 2003, Plaintiff was discharged from the hospital with instructions to continue anticoagulation therapy (*i.e.,* blood thinners), including Lovenox injections[4] and Warfarin. *Id.* at 11. Plaintiff has been advised by her doctors that she must

[2] Dr. Richart notes, "She initially attributed her leg discomfort to her student teaching activities and her shortness of breath to a presumed upper respiratory tract infection for which she was prescribed amoxicillin. There are no drug interactions between amoxicillin and the hormones in NuvaRing®." *See* Exhibit 2, at 10.

[3] Anticoagulation medications are those that make the blood less likely to form blood clots, and are popularly referred to as "blood thinners". *See* Exhibit 2 at 10-11.

[4] After being discharged from the hospital, Mrs. Prather personally administered Lovenox injections for approximately two weeks. Once Mrs. Prather's blood reached a certain therapeutic level after continued use of Warfarin, the Lovenox injections were discontinued. *See* Exhibit 2 at 11; Deposition of Marianne Prather, June 10, 2010, at 101:14-19, attached hereto as Exhibit 4.

continue taking Warfarin indefinitely (*i.e.,* for the remainder of her life). *Id.* at 12; Deposition of Marianne Prather, June 10, 2010, at 107:18-108:8, 111:17-22, attached hereto as Exhibit 4.

Plaintiff's injuries have severely affected her quality of life and forced her to permanently modify her routine and lifestyle due to her inherent, increased risk of trauma and bleeding associated with her previous injuries and continuing anticoagulation therapy. *See* Exhibit 3 at 209:2-14. Due to her lifelong anticoagulation therapy, Plaintiff has to attend frequent appointments, bi-weekly or at least monthly, to draw blood so that her doctor is able to closely monitor her INR levels[5]. *See* Exhibit 2 at 12; Exhibit 4 at 102:11-21. Mrs. Prather has been placed on dietary and medication restrictions due to the fact that many foods and medications interact negatively with Warfarin. *See* Exhibit 2 at 12; Exhibit 4 at 97:19-24, 134:13.

In light of her increased risk of injury and bleeding, Plaintiff is no longer able to perform regular household chores, such as climbing a ladder, or enjoy the active lifestyle that she used to before her injury, such as participating in recreational activities and playing softball. *See* Exhibit 2 at 12; Exhibit 4 at 131:25-17. In fact, the odds of Plaintiff suffering a major bleeding episode are quite high. Because she was only 33-years-old when placed on Warfarin and there is an approximate 1.3% per year risk of a major bleeding event while taking Warfarin[6], Plaintiff's cumulative lifetime risk of a major bleeding episode is 62.4%, assuming she would live to be 81 years old. *See* Exhibit 2 at 12.

Additionally, Plaintiff is unable to use combination hormonal contraceptives and has been advised that she and her husband should use condoms instead. *See* Exhibit 4 at 113:16-22, 114:18-21. Further, Plaintiff has been advised by her doctors that it is their recommendation that

[5] Warfarin doses change based on the particular patient's INR levels. *See* Exhibit 2 at 12.

[6] This information was derived by Dr. Richart from his review of a consultation note authored by Dr. Kraetsch, Plaintiff's treating hematologist.

she avoid future pregnancies, which is unfortunate because she and her husband had wished to have a third child. *See* Exhibit 2 at 12; Exhibit 4 at 114:1-8, 132:18-24, 133:14-17.

III. APPLICABLE LEGAL STANDARD

The Supreme Court mandates that the district court exercise its responsibility in acting as the "gatekeeper" for expert testimony. *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 588 (1993); *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 141 (1999). Thus, trial courts have broad discretion to admit or exclude expert testimony under Rule 702.[7] Accordingly, in order for an expert witness to testify, the district court must first determine the proposed testimony is (1) scientific, technical, or other specialized knowledge (2) that will assist the trier of fact to understand the evidence or to determine a fact in issue. *See Daubert*, 509 U.S. at 592; *Kumho*, 526 U.S. at 142.

In performing its "gatekeeper" role, the district court must determine whether the proposed expert testimony meets three prerequisites, which examines the expert's testimony for both reliability and relevance. *See Lauzon v. Senco Prods., Inc.*, 270 F.3d 681, 686 (8th Cir. 2001); *see also Marmo v. Tyson Fresh Meats*, 457 F.3d 748, 757-58 (8th Cir. 2006) (stating that an expert's testimony is relevant when "the reasoning or methodology in question is applied properly to the facts in issue", and an expert's testimony is reliable when "the expert is qualified to render the opinion and that the methodology underlying his conclusions is scientifically valid"). First, the expert's testimony "must be useful to the finder of fact in deciding the ultimate

[7] Rule 702 of the Federal Rules of Evidence governs the admission of expert testimony:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

FED.R.EVID. 702. Rule 702 codifies the standard set forth in *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579 (1993). *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147-49 (1999); *Hickerson v. Pride Mobility Prods. Corp.*, 470 F.3d 1252, 1258 n.3 (8th Cir. 2006).

issue of fact." *Lauzon*, 270 F.3d at 686. Second, the proposed expert "must be qualified to assist the finder of fact" by having "scientific, technical, or other specialized knowledge." *Id.* Third, the expert's testimony "must be reliable or trustworthy in an evidentiary sense, so that, if the finder of fact accepts it as true, it provides the assistance the finder of fact requires." *Id.* (internal quotation marks and citations omitted).

Although the court serves a gatekeeping function, "[t]he inquiry envisioned by Rule 702 … is a flexible one." *Bonner v. ISP Technologies, Inc.*, 259 F.3d 924, 929 (8th Cir. 2001) (quoting *Daubert*, 509 U.S. at 594-95). In particular, it is clear that "[d]etermining the validity of an expert's conclusions is the duty of the finder of fact." *Id.* Thus, the gatekeeper role, while essential, is not intended to supplant the adversary system or the role of the jury. Rather, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Robinson v. GEICO Gen. Ins. Co.*, 447 F.3d 1096 (8th Cir. 2006) (quoting *Daubert*, 509 U.S. at 596); *see also United States v. Davis*, 103 F.3d 660, 674 (8th Cir. 1996) (noting that the defendant was "free to challenge the expert's conclusions and point out the weaknesses of the [expert's] analysis to the jury during cross-examination" but "[w]eight and credibility are the province of the jury"); *Loudermill v. Dow Chem. Co.*, 863 F.2d 566, 570 (8th Cir. 1999) ("As a general rule, the factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility, and it is up to the opposing party to examine the factual basis for the opinion in cross examination."). Furthermore, "[c]ourts should resolve doubts regarding the usefulness of an expert's testimony in favor of admissibility." *Lauzon*, 270 F.3d at 785 (citing *Clark v. Heidrick*, 150 F.3d 912, 915 (8th Cir. 1998)).

IV. LEGAL ARGUMENT

A. Dr. Richart's Testimony Will Be Useful to the Jury.

The first requirement is that the expert's testimony "must be useful to the finder of fact in deciding the ultimate issue of fact." *Lauzon*, 270 F.3d at 686. Dr. Richart is Plaintiff's sole expert witness testifying that Ms. Prather's use of NuvaRing® caused her to suffer a pulmonary embolism. Clearly, Dr. Richart's causation testimony is necessary to assist the jury in deciding whether NuvaRing® caused Plaintiff's pulmonary embolism due to the fact that his opinions encompass medical opinions and observations not obvious to a layperson. *See e.g.*, *Menz v. New Holland North America, Inc.*, 507 F.3d 1107, 1111 (8th Cir. 2007) ("[Expert] testimony is necessary… "where the lay jury [does] not possess the experience or knowledge of the subject matter sufficient to enable them to reach an intelligent opinion without help."); *Clark*, 150 F.3d at 915 (holding that the rule favors admissibility if the testimony will assist the trier of fact); *Hoppe v. Midwest Conveyor Co.*, 485 F.2d 1996, 1202 (8th Cir. 1973) ("An expert witness is called primarily to aid the trier of fact in understanding evidence which is of a highly technical nature."). Moreover, doubts regarding an expert's testimony should be resolved in favor of admissibility. *See Miles v. GMC,* 262 F.3d 720, 724 (8th Cir. 2001) ("[D]oubts regarding whether an expert's testimony will be useful should generally be resolved in favor of admissibility."); *Arcoren v. United States,* 929 F.2d 1235, 1239 (8th Cir. 1991) ("The rule clearly is one of admissibility rather than exclusion.").

Here, Dr. Richart will be instrumental and absolutely necessary in helping the jury understand the case. It is clear that in the absence of expert witness testimony, the issue of medical causation is complicated and beyond the understanding of a layperson. In particular, Dr. Richart's testimony and causation opinions involve his analysis of Plaintiff's medical history, injuries, and risk factors, epidemiology literature and information pertaining to the increased risk

of venous thromboembolism associated with NuvaRing® as a third generation hormonal contraceptive, and information pertaining to hematologic parameters, which are issues and concepts that are not obvious to a layperson. As a result, without the testimony of Dr. Richart, a layperson will not fully understand the important issues pertaining to medical causation that are involved in this case.

Therefore, it is clear that Dr. Richart's testimony is necessary to assist the jury in understanding these complicated issues involving medical causation.

B. Dr. John Richart is Well-Qualified to Offer Expert Testimony Regarding Medical Causation.[8]

The second requirement is that the proposed expert "must be qualified to assist the finder of fact" by having "scientific, technical, or other specialized knowledge." *Lauzon*, 270 F.3d at 686. Dr. John Richart received his M.D. at the University of Missouri-Columbia. *See* Exhibit 1 at ¶2; Curriculum Vitae of Dr. John Richart, at 1, attached hereto as Exhibit 5. He is a licensed medical doctor and a Board Certified Hematologist. *See* Exhibit 1 at ¶3; Exhibit 2 at 1. He is also a member of various medical organizations, including the American Society of Hematology. *See* Exhibit 5 at 1. Currently, Dr. Richart serves as an Associate Professor of Medicine in the Division of Hematology and Oncology at Saint Louis University School of Medicine. *Id.* at 1-2; Exhibit 1 at ¶4.

In particular, Dr. Richart has over thirteen years of clinical experience in the management of bleeding and thrombotic disorders, both in the inpatient and outpatient setting. *See* Exhibit 2 at 1; Exhibit 1 at ¶5. During the course of his career, Dr. Richart has treated hundreds of patients with venous thromboembolism, including many women of childbearing age using hormonal contraceptives. *See* Deposition of John Richart, Oct. 21, 2011, at 103:24-104:10, attached hereto

[8] It should be noted that Defendants do not challenge Dr. Richart's qualifications.

as Exhibit 6. With regard to hormonal contraceptives, Dr. Richart has experience prescribing hormonal contraceptives to patients, albeit for purposes besides contraception. *Id.* at 90:22-91:12. Thus, Dr. Richart has the necessary expertise in the area of hormonal contraceptives as they relate to thrombosis to render medical causation opinions. *Id.* at 90:18-21.

Based on his education, training and over thirteen years of clinical experience as a medical doctor and treating hematologist, Dr. Richart is well-qualified to render an opinion in the present case as to the likely cause of Plaintiff's pulmonary embolism.

C. Dr. Richart's Medical Causation Opinions Are Reliable and Based on Sound Methodology.

Third, the expert's testimony "must be reliable or trustworthy in an evidentiary sense, so that, if the finder of fact accepts it as true, it provides the assistance the finder of fact requires." *Lauzon*, 270 F.3d at 686. To that end, the Court's focus must be on the expert's *principles* and *methodology*, rather than the *conclusions* generated. *See Daubert*, 509 U.S. at 595; *see also Polski v. Quigley Corp.*, 538 F.3d 836 838 (8th Cir. 2008) ("[T]he trial court must make a preliminary assessment of whether the *reasoning* or *methodology* underlying the testimony is scientifically valid.") (emphasis added) (internal quotation marks omitted)).

Defendants assert that the basis for Dr. Richart's opinion is nothing more than 'temporal proximity.'[9] However, such an assertion is absolutely incorrect. *See* Exhibit 1 at ¶7. In actuality, Dr. Richart's medical causation opinions are based on a proper differential diagnosis. It is well-established in the Eighth Circuit that a medical opinion about causation, based on a proper

[9] Despite the fact that Dr. Richart's expert opinion is based on a proper differential diagnosis, it is notable that under some circumstances, a strong temporal connection is powerful evidence of causation. *See Bonner v. Isp Techs.*, 259 F.3d 924, 929 (8th Cir. 2001) (citing *Heller v. Shaw Indus.*, 167 F.3d 146, 154 (3d Cir. 1999) ("if a person were doused with chemical X and immediately thereafter developed symptom Y, the need for published literature showing a correlation between the two may be lessened")).

differential diagnosis, is sufficiently reliable to satisfy *Daubert* and Rule 702. *See e.g., Turner*, 229 F.3d at 1208; *Bland*, 538 F.3d at 897; *Campbell*, 2011 U.S. Dist. LEXIS 59099 at *6.

Differential diagnosis is a technique utilized by medical experts whereby the cause of a medical condition is ascertained by eliminating the likely causes until the most probable cause is isolated. *See Turner*, 229 F.3d at 1208 (citing *Westberry*, 78 F.3d at 262-63). "The final result of a differential diagnosis is the expert's conclusion that a defendant's product caused (or did not cause) the plaintiff's injury." *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001). Differential diagnosis provides a valid foundation for admitting an expert opinion based on the fact that "a differential diagnosis is a tested methodology, has been subjected to peer review/publication, does not frequently lead to incorrect results, and is generally accepted in the medical community." *See Turner*, 229 F.3d at 1208.

As discussed in further detail below, Dr. Richart's medical causation opinions are based on a proper differential diagnosis and are thus sufficiently reliable to satisfy *Daubert* and Rule 702.

i. Dr. Richart's Medical Causation Opinions Are Based on Extensive Information, Facts, Literature and Data.

Dr. Richart's medical causation opinions are based on his review of an immense amount of materials. In particular, Dr. Richart thoroughly reviewed and considered relevant facts, data and information, including but not limited to Plaintiff's medical records and history, pertinent medical and scientific literature, relevant epidemiology literature regarding NuvaRing® and other combination hormonal contraceptives, clinical trials, product labeling, internal documents, as well as the deposition transcripts of Plaintiff, Plaintiff's prescribing physician and Plaintiff's treating physician. *See* Exhibit 1 at ¶9; Exhibit 2; Exhibit 3 at 170:13-24, 190:9-14; Supplemental Appendix A of Dr. John M. Richart ("Materials Reviewed"), attached hereto as

Exhibit 7. Dr. Richart then combined his review of these numerous resources with his knowledge, training, and over thirteen years of clinical practice and experience as a medical doctor and practicing hematologist to properly utilize the technique of differential diagnosis in the formation of his medical causation opinions.

In particular, Dr. Richart reviewed Plaintiff's extensive medical records from numerous medical providers[10] and the deposition transcripts of Plaintiff, Plaintiff's prescribing physician (Dr. Evelyne Schuetz) and Plaintiff's treating hematologist (Dr. Robert Kraetsch) in order to properly consider all relevant information regarding Plaintiff's injury, medical history, family history, genetic factors and other relevant risk factors for venous thromboembolism. *See generally* Exhibit 2; Exhibit 3 at 170:13-24, 190:9-14; Exhibit 7; Exhibit No. 9 of Deposition of Dr. John Richart, Nov. 18, 2011, attached hereto as Exhibit 8.

In addition, Dr. Richart reviewed relevant product labeling, internal documents and clinical trials for NuvaRing®. *See generally* Exhibit 2; Exhibit 7. Dr. Richart also conducted a fully independent analysis by considering the APCr and SHBG literature, as well as the epidemiology literature regarding the risk of venous thromboembolism associated with different types of hormonal contraceptives. Overall, Dr. Richart reviewed over 100 articles regarding several topics, including but not limited to the impact that hormonal contraceptives have on the clotting cascade, the APCr test and SHBG measurements. *See generally* Exhibit 2; Exhibit 7.

Therefore, it is clear that Dr. Richart thoroughly reviewed an extensive amount of materials and data in utilizing the technique of differential diagnosis to form the basis of his medical causation opinions, as discussed in further detail below.

[10] Medical records reviewed by Dr. Richart include the following: (1) Missouri Cancer Care (treating physician, Dr. Kraetsch); (2) Boonelick Medical Group (prescribing physician, Dr. Schuetz); (3) Raymond Hu; (4) Yelen Poborozhansky; (5) SSM St. Joseph's Health Center; (6) Barnes Jewish Hospital; (7) St. John's Mercy Medical Center; (8) Midwest ENT; (9) Walgreens Pharmacy; (10) Supplemental Walgreens Pharmacy. *See* Exhibit 9 of Deposition of Dr. John Richart, Nov. 18, 2011, attached hereto as Exhibit 8.

ii. Dr. Richart's Medical Causation Opinion is Based on a Proper Differential Diagnosis and Is Sufficiently Reliable Under* Daubert *and Rule 702.

In order for an expert's medical causation opinion – based on a proper differential diagnosis – to be sufficiently reliable under *Daubert* and Rule 702, an expert is required to "rule in" the suspected cause, as well as "rule out" other possible causes. *See e.g., Turner*, 229 F.3d at 1209 (citing *National Bank of Commerce of El Dorado v. Associated Milk Producers, Inc.*, 191 F.3d 858 (8th Cir. 1999)); *Junk v. Terminix Intern. Co.*, 628 F.3d 439, 449 (8th Cir. 2010) (citing *Kudabeck v. Kroger Co., 338 F.3d* 856, 860-61 (8th Cir. 2003)). A medical expert begins by "ruling in" all scientifically plausible causes of the plaintiff's injury, and then "ruling out" the least plausible causes of injury until the most likely cause remains. *See Glastetter*, 252 F.3d at 989. *That is precisely what Dr. Richart did here.*

As discussed below, Dr. Richart began by "ruling in" all plausible causes:

1. Plaintiff's Contraceptive Use

Dr. Richart considered Plaintiff's previous use of contraceptives, as well as her current use of NuvaRing® at the time of her injury. In terms of her previous use of contraceptives, Dr. Richart noted that Plaintiff had been "on oral contraceptive pills on and off since age 18 secondary to irregular menses (periods)." *See* Exhibit 2 at 12. He also noted that in 1992 she used Norinyl 1/35, a first generation progestin delivering 1 mg of norethindrone and 0.035 mg of estradiol. *Id.* In 1994, she began using Desogen, which delivers 0.15 mg of desogestrel (a third generation progestin) and 0.03 mg of ethinyl estradiol. *Id.* He noted that she later discontinued Desogen, but was restarted on Desogen after the delivery of her first child in 1997. *Id.* Dr. Richart noted that Plaintiff again discontinued her use of Desogen in 1998, during which time she had her second child in 2002. *Id.*

On August 13, 2003, Plaintiff received a prescription for NuvaRing®. *See* Exhibit 2 at 2.

NuvaRing® contains the progestin, etonogestrel, the active metabolite of desogestrel, and therefore is considered to be a third generation hormonal contraceptive with a vaginal route of administration (in comparison to a pill). *Id.* at 3. Because Plaintiff had to wait until her period finished before starting NuvaRing®, and the office note from August 25, 2003, lists NuvaRing® as a current medication, this would most likely be Plaintiff's first week of using NuvaRing®. *Id.* The ring would be inserted for a period of three weeks and then removed for one week before inserting a new ring. *Id.* As a result, Plaintiff would have started her second cycle of NuvaRing® in late September. *Id.* Thus, Plaintiff used NuvaRing® up until the time she suffered her pulmonary embolism on October 4, 2003, which was within 2 cycles of her NuvaRing® use. *Id.* at 12, 15.

2. Plaintiff's Age

Dr. Richart noted that Plaintiff was thirty-three (33) at the time she suffered her venous thromboembolism. *See* Exhibit 2 at 10.

3. Plaintiff's Weight

Dr. Richart noted that Plaintiff was 'overweight' – *not obese* – at the time of her venous thromboembolism due to the fact that her body mass index (BMI) was above 25 kg/m2, but below 30 kg/m2. *See* Exhibit 2 at 13; Exhibit 3 at 206:1-3. Dr. Richart further noted that a BMI of 31 kg/m2 was recorded on September 15, 2002, which is classified as 'obese' (30-39.9 kg/m2). *See* Exhibit 2 at 13. However, Dr. Richart noted that she was actually bumped into the 'obese' category at this time after she had her second baby, but that she later lost weight and her BMI returned to the 'overweight' category. *See* Exhibit 3 at 245:10-13.

4. Plaintiff's Pregnancies

Dr. Richart noted that Plaintiff has had two normal spontaneous vaginal deliveries on

March 12, 1997 and July 24, 2002. *See* Exhibit 2 at 13.

5. Plaintiff's Blood Type

Dr. Richart noted that Plaintiff's blood type is type A. *See* Exhibit 2 at 11; Exhibit 3 at 183:15-17.

6. Other Aspects of Plaintiff's Past Medical History

Dr. Richart noted that Plaintiff has a history of depression (began taking antidepressant medications on December 6, 2008), exercise induced asthma (which was worse in childhood), and hypercholesterolemia (began taking cholesterol lowering medication on October 11, 2004). *See* Exhibit 2 at 12. In terms of Plaintiff's past surgical history, Dr. Richart noted that she underwent an arthroscopy with menisectomy for "bucket handle tear" of the medial meniscus on September 24, 1987, endoscopic antrostomies and ethmoidectomies for chronic sinusitis on April 27, 2000, and apparent anterior cruciate ligament repair of the knee on March 6, 2008. *Id.*

7. Plaintiff's Genetic Testing

Dr. Richart noted that Plaintiff was found to be homozygous for the C677T mutation of methyl tetrahydrofolate reductase (MTHFR)[11]. *See* Exhibit 2 at 11. However, he noted that Plaintiff had a normal homocysteine level. *Id.* Next, Dr. Richart noted that Plaintiff was found to be heterozygous for the G20210A Prothrombin gene mutation.[12] *Id.* Dr. Richart then noted that Plaintiff was found to have a normal Factor VIII level for blood type A. *Id.* Finally, Dr. Richart noted that Plaintiff tested negative for Factor V, antiphospholipid antibodies, Protein S, and Protein C deficiency. *Id.* at 12.

[11] As Dr. Richart explains, "The C677T mutation of MTHFR can potentially lead to elevated homocysteine levels in the blood (hyperhomocysteinemia). Homocysteine is an amino acid and a normal building block for the synthesis of proteins. Elevated blood levels of homocysteine can lead to blood vessel damage, as well as venous and arterial thrombotic events." *See* Exhibit 2, at 11.

[12] As Dr. Richart explains, "Prothrombin is the clotting factor that initiates the final common pathway of blood clot formation. Having this mutation leads to increased levels of prothrombin." *See* Exhibit 2, at 11.

8. Plaintiff's Family History

Dr. Richart also took into account that, according to Plaintiff, her father was diagnosed with phlebitis when Plaintiff was a child.[13] *See* Exhibit 2 at 13. Dr. Richart also considered the fact that her father has suffered transient ischemic attacks, has coronary artery disease (heart disease), and has underwent bypass surgery. *Id.* at 13. After evaluating the genetic testing results of Plaintiff and her immediate family, Dr. Richart believes that Mrs. Prather's father must be at least heterozygous for the C677T MTHFR mutation – although he may be homozygous or even compound heterozygous for this gene. *Id.* He also believes that Mrs. Prather's father may be heterozygous for the Factor V Leiden mutation, which leads to activated Protein C resistance and is the most common hereditary thrombophilia. *Id.* Lastly, Dr. Richart believes that Plaintiff's father may be heterozygous for the Prothrombin gene mutation. *Id.*

As for Plaintiff's mother, Dr. Richart noted that she has not experienced a deep vein thrombosis or pulmonary embolism. *See* Exhibit 2 at 14. However, based on Plaintiff's genetics, Dr. Richart believes that she must be at least heterozygous for the C677T MTHFR mutation, or

[13] Defendants note a potential discrepancy between the deposition testimony of Plaintiff and the deposition testimony of Mrs. Prather's father regarding this issue. During Plaintiff's deposition, she testified that her father was diagnosed with phlebitis while in the hospital for another condition. *See* Exhibit 2 at 13; Exhibit 4 at 34:1-11. However, Defendants argue that Plaintiff's father testified during his deposition that he was hospitalized with a blood clot and received anticoagulation therapy. *See* Defs' Motion, at 4. Dr. Richart testified that he reviewed the deposition testimony of Plaintiff and relied on Plaintiff's self-reporting regarding her family history during her deposition. *See* Exhibit 3 at 220:13-16; 232:11-22. It is clear that any purported inaccuracies in Plaintiff's self-reporting should not be detrimental to the expert's opinion; rather, such purported inaccuracies can be explored through cross-examination. *See Walker v. Soo Line R. Co.*, 208 F.3d 581, 586-87 (7th Cir. 2000) ("Medical professionals reasonably may be expected to rely on self-reported patient histories. Such histories provide information upon which physicians may, and at times must, rely in their diagnostic work. Of course, it is certainly possible that self-reported histories may be inaccurate. [The expert] said that it was not unusual for patients to misrepresent their histories to him. In situations in which a medical expert has relied upon a patient's self-reported history and that history is found to be inaccurate, district courts usually should allow those inaccuracies in that history to be explored through cross-examination); *Abernathy v. Union Pac. R.R. Co.*, 2011 U.S. Dist. LEXIS 41931, *7 (E.D. Ark. Apr. 13, 2011) ("[A]ny inaccuracies in Plaintiff's self-reported history can be explored through cross-examination."); *see also Daubert*, 509 U.S. at 596 ("Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence."). Where, as here, Dr. Richart has used a reliable method to reach his medical opinion about causation, based on a proper differential diagnosis, any potential inaccuracies in Plaintiff's self-reporting, *if there are in fact any*, do not warrant the exclusion of plainly relevant and reliable expert testimony.

possibly homozygous or compound heterozygous. *Id.* Dr. Richart further believes that Plaintiff's mother may be heterozygous for the Factor V Leiden mutation and the Prothrombin gene mutation. *Id.*

As for Plaintiff's two sisters, Dr. Richart noted that the first sister has two hereditary thrombophilias – in particular she is heterozygous for the Factor V Leiden mutation and is a compound heterozygote for MTHFR genes with hyperhomocysteinemia. *See* Exhibit 2 at 14. However, despite having these two hereditary thrombophilias, she has never experienced a deep vein thrombosis or pulmonary embolism. *Id.* at 14. Dr. Richart noted that the second sister has antiphospholipid antibody syndrome ("APLS"), which is an autoimmune disease where the immune system makes proteins that attack normal tissues and can lead to both arterial and venous thrombotic events. *Id.* In fact, it was this second sister, diagnosed with APLS, who suffered a deep vein thrombosis. *See* Exhibit 3 at 227:4-10.

9. Epidemiology Literature - Hormonal Contraceptives and VTE Risk

Dr. Richart reviewed an extensive number of epidemiology articles examining the risk of venous thromboembolism associated with hormonal contraceptives containing different progestins (*i.e.,* second generation progestins and third generation progestins). *See* Exhibit 1 at ¶9. In total, Dr. Richart reviewed well over 100 epidemiology articles examining this issue, including articles indicating that third generation hormonal contraceptives are associated with an increased risk of VTE, as well as articles demonstrating no difference in VTE risk between second and third generation hormonal contraceptives. *See* Exhibit 6 at 146:8-20, 150:10-151:18, 198:8-201:6, 208:9-19, 229:2-18, 233:15-235:3, 238:21-239:14, 241:24-242:17, 253:3-254:4; *see also* Exhibit 7.

It is important to note that at the time Dr. Richart prepared his Report, there were no published epidemiological studies concerning NuvaRing® specifically. *See* Exhibit 1 at ¶10; Exhibit 2 at 3. However, after Dr. Richart prepared his Report, additional epidemiology studies were published that Dr. Richart has now reviewed in further support of his opinions that *NuvaRing® users*, in comparison to users of safer alternatives, are at an increased risk of venous thromboembolism. *See* Exhibit 1 at ¶¶10-12; FDA Office of Surveillance and Epidemiology, KPNC, KPSC, Vanderbilt University, Washington University (2011), Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints (FDA/Kaiser Study), attached hereto as Exhibit 9; Lidegaard Ø., *et al.* (2012), Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10, *British Medical Journal*, 344:e2990, attached as Exhibit 10; Lidegaard, *et al.* (2012), Thrombotic stroke and myocardial infarction with hormonal contraception, *New England Journal of Medicine*, 366:2257-66, attached hereto as Exhibit 11. In particular, one of these recent published studies, *which was not funded by Merck,* found that after examining data on more 1.6 million Danish women, users of NuvaRing® had nearly *double the risk* of suffering venous thromboembolism than users of second generation products. *See* Exhibit 1 at ¶10; Exhibit 11.

10. Information and Literature Regarding Hematological Parameters

Dr. Richart noted that hormonal contraceptives induce many changes in coagulation factors – the net effect of which is prothrombotic – and prothrombotic changes have been observed in the resistance to activated protein C, which provides a biological mechanism for hormone induced hypercoagulation. *See* Exhibit 2 at 5. APC resistance is associated with decreases in protein S activity and TFPI caused by estrogen and these changes are associated with increased VTE risk. *Id.* In measuring these prothrombotic changes associated with VTE

risk, the Rosing Test, which has been validated, is more sensitive than the clotting based assay. *Id.*

Dr. Richart conducted his own independent review of various coagulation studies that measured changes in clotting factor levels, finding that third generation hormonal contraceptives induce a prothrombotic change above that of second generation hormonal contraceptives.[14] *See generally* Exhibit 2; Exhibit 7. One study specific to NuvaRing® (known as the "MENs Study") demonstrated an increase in APCr and SHBG for NuvaRing® users, thus confirming a higher association of VTE risk in NuvaRing® users as compared to users of second generation hormonal contraceptives containing levonorgestrel. *See* Exhibit 2 at 9.

11. Clinical Trials Involving NuvaRing®

Dr. Richart reviewed two clinical studies performed by Organon, Clinical Trials 34220 and 34221,[15] pertaining to procoagulation variables specific to NuvaRing®. *See* Exhibit 2 at 5-6. These studies reported a statistically significant increase in SHBG as compared to the LNG/EE group, which was confirmed in the independent MENs Study. *Id.* at 9. Clinical Trial 34218 shows that NuvaRing® delivers etonogestrel and ethinyl estradiol in wide variability to each other, including wide variability of the estrogen dose between users, as well as variability of the estrogen dose throughout the cycle. *Id.* at 10.

[14] *See e.g.,* Rosing, *et al.* (1997), Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second- and third-generation oral contraceptives, *British Journal of Hematology*, 97:233-38, attached hereto as Exhibit 12; Tschaikovski & Rosing (2010), Mechanisms of estrogen-induced venous thromboembolism, *Thrombosis Research*, 126:5-11, attached hereto as Exhibit 13; Tans, *et al.* (2003), Activated protein C resistance determined with a thrombin generation-based test predicts for venous thrombosis in men and women, *British Journal of Hematology*, 122:465-70, attached hereto as Exhibit 14; de Visser, *et al.* (2005), Determinants of the APTT- and ETP-based APC sensitivity tests, *Journal of Thrombosis and Haemostasis*, 3:1488-94, attached hereto as Exhibit 15; Van Vliet, *et al.* (2004), Prothrombotic changes in users of combined oral contraceptives containing drospirenone and cyproterone acetate, *Journal of Thrombosis and Haemostasis*, 2:2060-62, attached hereto as Exhibit 16.

[15] Notably, Organon did not test APCr levels in NuvaRing® in this clinical study. *See* Exhibit 2 at 6.

After "ruling in" these possible causes, Dr. Richart then "ruled out" potential causes, as discussed below:

1. Plaintiff's Contraceptive Use

It is clear that Dr. Richart considered Plaintiff's previous use of contraceptives, including her use of Desogen, which contains a third generation progestin. In fact, Dr. Richart noted that Plaintiff used Desogen, which contains a third generation progestin, both before and after having her second child, without experiencing any problems. *See* Exhibit 3 at 214:17-23. However, Plaintiff never experienced any thromboembolic complications until she began using NuvaRing® in 2003. *See* Exhibit 2 at 14. Although Dr. Richart noted that the use of hormonal contraceptives places a woman at an increased risk of suffering a venous thromboembolism, Dr. Richart concluded that Plaintiff was at an *even greater risk* of suffering venous thromboembolism while using NuvaRing® due to its novel delivery system, wide range of variability in terms of its delivered dose of estrogen, and higher pro-thrombotic effect as evidenced by hematologic parameters. *See* Exhibit 2 at 2, 7, 9-10.

2. Plaintiff's Age

Dr. Richart concluded that Plaintiff was not at a clinically significant increased risk of venous thromboembolism due to the fact that she was thirty-three (33) at the time of her injury. *See* Exhibit 3 at 243:2-11.

3. Plaintiff's Weight

After examining Plaintiff's medical records, Dr. Richart concluded that she was overweight – *not obese* – while using NuvaRing®, and in fact Plaintiff was overweight while using other combined hormonal contraceptives, with the exception of one instance. *See* Exhibit 2 at 13; Exhibit 3 at 215:11-216:1, 244:1-8. In particular, Dr. Richart noted that a BMI of 31

kg/m2 was recorded on September 15, 2002, which is classified as 'obese' (30-39.9 kg/m2). *See* Exhibit 2 at 13. However, Dr. Richart noted that she was actually bumped over into the 'obese' category after she had her second baby, but that she later lost weight resulting in her BMI returning to the 'overweight' category, which is where she remained up until the time she began using NuvaRing® and suffered her venous thromboembolism. *See* Exhibit 3 at 245:10-13. Therefore, Mrs. Prather's weight was not significantly different during her use of other combined hormonal contraceptives over the six years prior to her venous thromboembolism. *See* Exhibit 3 at 245:6-15.

4. Plaintiff's Pregnancies

Dr. Richart testified that pregnancy and postpartum places a woman at a thrombotic state, and the peripartum carries a greater risk than pregnancy. *See* Exhibit 3 at 180:11-181:4. Nonetheless, Plaintiff did not experience any thrombotic events during either one of her two pregnancies or during her respective postpartum periods, despite the fact that pregnancy and postpartum places a woman at an increased risk of venous thromboembolism. *Id.* These were additional facts specific to Mrs. Prather's case that Dr. Richart considered in reaching his medical opinions regarding the cause of Mrs. Prather's pulmonary embolism.

5. Plaintiff's Blood Type

Dr. Richart noted that Factor VIII levels are blood type dependent, meaning that the normal range of Factor VIII is different depending on the blood type of the individual. *See* Exhibit 2 at 11. Dr. Richart concluded that Mrs. Prather had a normal Factor VIII level for blood type A. *Id.* at 11-12. Dr. Richart recognized that one study indicated that the age-adjusted odds ratio of VTE for non-O blood type was 1.64. *See* Exhibit 3 at 181:17-182:20. However, Dr. Richart concluded that non-O type blood and a thrombophilia, such as Prothrombin gene

mutation, are independent factors – *not multiplicative factors* – in regard to VTE risk. *See* Exhibit 3 at 183:15-184:11.

6. Other Aspects of Plaintiff's Past Medical History

Dr. Richart noted that women with high cholesterol receiving hormonal supplementation have an increased risk of arterial thrombotic events. *See* Exhibit 3 at 217:3-218:3. However, Dr. Richart concluded Plaintiff's cholesterol was not relevant in determining causation in this particular case because she did not suffer an *arterial* thrombotic event – she suffered a *venous* thrombotic event. *Id.* Additionally, Dr. Richart concluded that the other factors considered did not place Plaintiff at a clinically significant increased risk of venous thromboembolism. *See* Exhibit 2 at 12-13.

7. Plaintiff's Genetic Testing

Although Plaintiff was found to be homozygous for the C677T mutation of methyl tetrahydrofolate reductase (MTHFR), Dr. Richart noted that carriers of the MTHFR C677T mutation are not at an increased risk for VTE if the homocysteine levels are normal.[16] *See* Exhibit 3 at 205:13-24. Because Mrs. Prather had normal homocysteine levels (*i.e.,* not elevated), Dr. Richart concluded that Mrs. Prather was not at an increased risk of venous thromboembolism. *See* Exhibit 2 at 11. Since the gene (MTHFR C677T) itself is not thrombophilic (rather the homocysteine levels are the determinative factor), Dr. Richart concluded that the MTHFR mutation was not relevant to the cause of Plaintiff's VTE. *Id.*; *see also* Exhibit 3 at 187:8-13.

Because Mrs. Prather was found to be heterozygous for the G20210A Prothrombin gene mutation, Dr. Richart noted that "heterozygous" refers to the fact that only one of the two copies

[16] Dr. Richart noted that it is not the gene that is thrombophilic, rather it is the homocysteine level that is thrombophilic.

of the gene is mutated, meaning that a "heterozygous" carrier has a decreased risk of VTE in comparison to a "homozygous" carrier. *See* Exhibit 3 at 203:24-204:6. As a result, a person who is heterozygous for the Prothrombin gene mutation is associated with a relative risk of VTE of 2.8 (meaning that populations carrying this mutation have nearly a threefold risk of developing VTE as compared to the normal population). *See* Exhibit 2 at 11. However, Dr. Richart concluded that although this mutation was present during her two pregnancies and prior contraceptive use, she did not develop a venous thromboembolism during any of those times. *See* Exhibit 3 at 261:8-24. Based on the fact that this genetic mutation did not cause a venous thromboembolism during any of her previous challenges, Dr. Richart concluded that it is highly unlikely that the Prothrombin gene mutation was a significant factor in causing her VTE, which she suffered while using NuvaRing®. *Id.* at 265:11-266:1.

8. Plaintiff's Family History

Dr. Richart concluded that Plaintiff's family history did not place Plaintiff at a higher risk than the normal population of developing a venous thromboembolism with the use of combined hormonal contraceptive agents. *See* Exhibit 2 at 14.

As for Plaintiff's father, Dr. Richart noted that, according to Plaintiff, he has not experienced a deep venous thrombosis or pulmonary embolism. *Id.* Neither phlebitis[17] nor thrombophlebitis[18] is considered a venous thromboembolism or deep vein thrombosis. *See* Exhibit 3 at 220:10-12, 222:17-24, 232:6-9. In fact, there is no evidence of hereditary thrombophlebitic syndrome. *Id.* at 222:11-16. Further, the father's medical history of *arterial* thrombotic events is not relevant to consider within the context of Plaintiff's injury she suffered

[17] Dr. Richart explained that "[p]hlebitis is an inflammation of a vein and is most often associated with trauma particularly in hospitals at sites of intravenous catheters." *See* Exhibit 2 at 13.

[18] Dr. Richart explained that thrombophlebitis is an inflammation of the vein with an associative superficial blood clot – not a deep vein thrombosis – that is typically associated with trauma or varicosities (*i.e.,* varicose veins). *See* Exhibit 3 at 221:16-222:10.

(*i.e., venous* thromboembolism). *Id.* at 231:24-232:5.

As for Plaintiff's second sister with antiphospholipid antibody syndrome ("APLS"), Dr. Richart concluded that it was her APLS that was likely a substantial contributing cause to the DVT suffered by Plaintiff's sister. *See* Exhibit 3 at 230:5-16. Dr. Richart notes that APLS is not a genetic issue – rather it is an *acquired* thrombophilic state. *Id.* at 225:19-23. Thus, the fact that Plaintiff's sister has APLS has nothing to do with the genetics of her immediate family members, including Plaintiff, because the condition is not hereditary. *Id.* at 226:14-21, 229:23-230:3. In fact, Plaintiff was tested for antiphospholipid antibodies and none were found. *See* Exhibit 2 at 14.

9. Epidemiology Literature - Hormonal Contraceptives and VTE Risk

Dr. Richart noted that in 1995 several large epidemiology studies were published indicating that combination oral contraceptives containing third generation progestins (such as the type of progestin contained in NuvaRing®, which contains etonogestrel – the active metabolite of desogestrel) were associated with an increased risk of VTE in comparison to hormonal contraceptives containing second generation progestins. *See* Exhibit 2 at 2. As a result, pharmaceutical companies (including the manufacturers of NuvaRing®) funded re-analyses of these original studies. *Id.* While the company-funded studies found no difference between third and second generation hormonal contraceptives, independent studies developed the consensus opinion that third generation hormonal contraceptives are associated with at least a two-fold increase in the risk of venous thromboembolism in comparison to second generation hormonal contraceptives. *Id.* at 2-3. In particular, this consensus opinion was confirmed in two large studies published in the *British Medical Journal* in 2009. *Id.* at 9. Dr. Richart reviewed later literature indicating that there is no difference in VTE risk between third and second generation

hormonal contraceptives, but found serious design flaws in these studies supporting that they should be rejected. *Id.*

After Dr. Richart's review of the epidemiology literature, which compared the VTE risk between second and third generation hormonal contraceptives, it is his opinion that third generation contraceptives, including NuvaRing®, are associated with an increased risk of VTE. *See* Exhibit 2 at 10. Dr. Richart's opinion is further supported by the fact that epidemiology literature now available and/or recently published (prior to the time he submitted his Report) specifically concerning NuvaRing® confirm that *NuvaRing® users*, in comparison to users of safer alternatives, are at an increased risk of venous and arterial thromboembolism. *See* Exhibit 1 at ¶¶10-12; Exhibit 9; Exhibit 10; Exhibit 11.

10. Information and Literature Regarding Hematological Parameters

With respect to the association between hematological markers and NuvaRing®, Dr. Richart notes that studies have reported differences in VTE risk between contraceptive products containing the same dose of estrogen, *but different progestins* – as discussed above. *See* Exhibit 2 at 2-3. The type of progestin relates to the relative anti-estrogenicity of the contraceptive product, and that together with the estrogen component, comprises the 'total estrogenicity.' *Id.* at 4. The anti-estrogenicity of third generation progestins (such as that contained in NuvaRing®) is less than second generation progestins. *Id.* Sex hormone binding globulin (SHBG)[19] is a putative marker of 'total estrogenicity' and is a potential surrogate marker for VTE risk related to estrogen exposure, which positively correlates with APC resistance. *Id.* at 4-5. Further, it is Dr. Richart's opinion that third generation progestins have increased total estrogenicity when

[19] SHBG is a steroid sensitive protein produced in the liver, which increases with estrogen exposure in a dose-dependent manner. *See* Exhibit 2 at 4.

compared to second generation hormonal contraceptives, and the thrombin generation based APC assay (*i.e.* Rosing Test) has been validated to be predictive of VTE risk. *Id.* at 5.

With that said, Dr. Richart concluded that the hemostasis literature is plentiful and a consensus has developed that APCr and SHBG changes in contraceptive users are markers indicative of higher VTE risk associated with COCs. *See* Exhibit 2 at 10. Although Organon did not test the changes in APCr in patients using NuvaRing®, an independent study ("MENs Study") has done so and confirms that NuvaRing® significantly increases APCr as compared to an LNG comparator hormonal contraceptive. *Id.*

11. Clinical Trials Involving NuvaRing®

Data from Clinical Trials 34220 and 34221 confirm that NuvaRing® is at least twice as thrombotic as LNG-containing hormonal contraceptives (*i.e.,* second generation hormonal contraceptives). *See* Exhibit 2 at 5-6. As for Clinical Trial 34218, because of the demonstrated variability leading to unopposed and underopposed estrogen, some users of NuvaRing® will be at an increased risk of VTE in comparison to users of hormonal contraceptives containing desogestrel, and this risk is variable because of the novel hormone delivery system of NuvaRing®. *Id.* at 9. Such an imbalance between the EE and the ENG creates a situation where the thrombotic effects of the EE are unopposed by the ENG, leading to a much more likely scenario for clotting. *Id.* at 7-9.

* * * *

In conclusion, there is ample evidence that Dr. Richart systematically ruled in and ruled out possible causes in opining, within a reasonable degree of medical certainty, that NuvaRing® was the most probable cause of Plaintiff's venous thromboembolism. In other words, after Dr. Richart "ruled in" all scientifically plausible causes of Plaintiff's injury, and "ruled out" the least

plausible causes of injury, the most likely cause - ***NuvaRing***® - remained. *See Glastetter*, 252 F.3d at 989. Because it is clear that a proper differential diagnosis is the basis for Dr. Richart's medical causation opinion, Defendants' assertion that Dr. Richart's opinion is based merely on 'temporal proximity' is completely without merit.

Although Dr. Richart systematically 'ruled in' and 'ruled out' an extensive list of possible causes, it is important to note that causation testimony should not be excluded on the basis that the expert witness has failed to rule out every possible alternative cause. *See Lauzon*, 270 F.3d at 693 (stating that the requirement of ruling out other possibilities "cannot be taken to a quixotic extreme."); *Turner*, 229 F.3d at 1208-09 (an expert opinion based on differential diagnosis is admissible when it identifies "the most probable cause"). It is clear that medical experts do not need to rule out *every* conceivable cause in order for their differential diagnosis based opinions to be admissible. *See e.g., Lauzon*, 270 F.3d at 693; *Westberry*, 78 F.3d at 266; *In re Paoli R.R. Yard PCG Litig.*, 35 F.3d 717, 764-65 (3d Cir. 1994). Defendants will have "the opportunity to expose the testimony's weaknesses through vigorous cross-examination and the presentation of contrary evidence." *In re Prempro Products Liability Litigation*, 586 F.3d 547, 567 (8th Cir. 2009) (citing *Daubert*, 509 U.S. at 596).

After systematically 'ruling in' and 'ruling out' all of these potential causes, and based upon his review of Plaintiff's medical history and extensive factual data, his review of pertinent materials pertaining to hematologic parameters, third generation contraceptives and NuvaRing®, and his vast experience as a medical doctor and treating hematologist, Dr. Richart concluded within a reasonable degree of medical certainty that Plaintiff's NuvaRing® use was a substantial contributing cause of her pulmonary embolism. *See* Exhibit 1 at ¶¶6, 13; Exhibit 2 at 14-16. Because Dr. Richart reviewed extensive evidence and systematically 'ruled in' potential causes

and 'ruled out' potential causes, Dr. Richart's causation opinion is based on a proper differential diagnosis. Therefore, Dr. Richart's causation opinion is sufficiently reliable to satisfy the requirements of *Daubert* and Rule 702.

iii. Defendants' Other Objections Are Without Merit.

Defendants' remaining criticisms constitute mere disagreements with the factual bases of Dr. Richart's opinions, *and if anything*, are matters for cross-examination. *See Larson v. Kempker*, 414 F.3d 936, 941 (8th Cir. 2005) ("As a general rule, the factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility, and it is up to the opposing party to examine the factual basis for the opinion in cross-examination"); *Kudabeck*, 338 F.3d at 861 ("[A]ttacks regarding the completeness of [a doctor's] methodology go to the weight and not the admissibility of his testimony.").

Further, any doubts regarding the usefulness of an expert's testimony should be resolved in favor of admissibility. *See Clark*, 150 F.3d at 915; *Campbell*, 2011 U.S. Dist. LEXIS 59099 at *8. "Although it is common that medical experts often disagree on diagnosis and causations, questions of conflicting evidence must be left for the jury's determination." *Hose v. Chicago Northwestern Transp. Co*., 70 F.3d 968, 976 (8th Cir. 1995); *see also Bonner*, 259 F.3d at 929 ("Our role is not to determine whether [the expert witness'] opinion was correct; that was for the jury to decide."). The only relevant question in regard to the *admissibility* of evidence is whether it is sufficiently reliable and relevant to assist the jury's determination of a disputed issue. *See Bonner*, 259 F.3d at 929 (citing *Daubert*, 509 U.S. at 594-95)).

First, Defendants argue that Dr. Richart's medical causation opinions should be excluded due to the lack of scientific literature he cites in support of his opinions. *See* Defs' Motion at 5-9. Second, Defendants argue that Dr. Richart's medical causation opinions should be excluded on

the basis that he is unable to render his medical causation opinions with absolute certainty. *Id.* at 7-8. However, as discussed below, both of Defendants' arguments are without merit and do not provide sufficient bases for exclusion.

1. Defendants' Argument that Dr. Richart's Opinions Should be Excluded due to his Failure to Cite Supporting Literature Is Baseless.

Defendants argue that the sole basis for Dr. Richart's medical causation opinion is a 'one patient cross over trial' methodology that has no support in the literature. *See* Defs' Motion at 1, 4. Although Dr. Richart did consider Plaintiff's past and current contraceptive use in conjunction with other data and risk factors, the fact that Plaintiff suffered a pulmonary embolism while on NuvaRing® was not the sole premise of his causation opinion – as Defendants incorrectly lead the Court to believe. It is true that Dr. Richart noted Plaintiff had all the same risk factors present during her two pregnancies and while using Desogen, which actually contains more estrogen in comparison to NuvaRing®, but that Plaintiff did not experience a thrombotic event until she began using NuvaRing®. *See* Exhibit 3 at 247:10-248:4. Dr. Richart also noted that there are important differences between NuvaRing® and Desogen that placed Mrs. Prather at an increased risk of VTE due to her NuvaRing® use. *Id.* at 249:8-23. ***However***, Dr. Richart did not consider Plaintiff's past and current contraceptive use in isolation from other data, literature, medical information and risk factors pertinent to consider in his differential diagnosis.

As discussed above, it is clear that Dr. Richart utilized the proper technique of differential diagnosis by systematically 'ruling in' and 'ruling out' an extensive list of potential causes in forming the basis of his medical causation opinion. Thus, Dr. Richart's medical causation opinion is not based solely on the fact that Plaintiff suffered her VTE while using NuvaRing®; rather, a multitude of facts, data, literature and information was systematically considered during his differential diagnosis. With that said, the fact that Dr. Richart referred to his approach as a

"one-patient cross-over trial" within his Report is completely irrelevant. The bottom line is that Dr. Richart reviewed sufficient evidence and systematically 'ruled in' potential causes and 'ruled out' potential causes, so that his medical causation opinions are based on sound methodology and thus sufficiently reliable to satisfy the requirements of *Daubert* and Rule 702.

In addition to Defendants' argument that Dr. Richart failed to cite literature supporting the 'one-patient cross-over trial', Defendants also argue that Dr. Richart cited no data or literature indicating that the VTE risk associated with NuvaRing® is different than the VTE risk associated with second-generation pills. *See* Defs' Motion at 9. Although there were no published epidemiology studies concerning NuvaRing® at the time Dr. Richart prepared his Report, it is important to note that epidemiology studies involving NuvaRing® are now available and/or have recently been published that Dr. Richart has reviewed and further support his opinion that *NuvaRing® users*, in comparison to users of safer alternatives, are at an increased risk of venous thromboembolism. *See* Exhibit 1 at ¶¶10-12; Exhibit 2 at 3; Exhibit 19; Exhibit 10; Exhibit 11.

With that said, it is clear that there is no requirement that published epidemiology studies supporting an expert's opinion must exist in order for an expert's opinion to be admissible. *See e.g., Bonner*, 259 F.3d at 929; *National Bank of Commerce*, 191 F.3d at 862. Likewise, there is no requirement that a medical expert must always cite published studies in order to render a reliable expert opinion regarding causation (*i.e.,* conclude that a particular product caused a particular injury). *See e.g., Turner*, 229 F.3d at 1208-09; *Kudabeck*, 338 F.3d at 862; *Bonner*, 259 F.3d at 929; *Heller v. Shaw Indus.*, 167 F.3d 146, 155 (3d Cir. 1999); *Westberry*, 78 F.3d at 262 (holding that a reliable differential diagnosis alone provides valid foundation for causation opinion, even when no epidemiological studies, peer-reviewed published studies, animal studies,

or laboratory data are offered in support of the opinion); *Paige v. Harper*, 1:06CV111 2010 U.S. Dist. LEXIS 1394 at *6 (E.D. Mo. Jan. 8, 2010).

"Even if the judge believes there are better grounds for some alternative conclusion, and that there are some flaws in the scientist's methods, if there are good grounds for the expert's conclusion, it should be admitted…. The district court could not exclude [scientific] testimony simply because the conclusion was 'novel' if the methodology and the application of the methodology were reliable." *Bonner*, 259 F.3d at 929 (citing *Heller*, 167 F.3d at 152-53). The primary concern of Rule 702, as made clear by the Supreme Court, is the expert witnesses' methodology, rather than their conclusion. *See Kumho*, 526 U.S. at 152; *Daubert*, 509 U.S. at 594-95.

Because Dr. Richart reviewed extensive evidence and systematically 'ruled in' potential causes and 'ruled out' potential causes, Dr. Richart's causation opinion is based on a proper differential diagnosis and is thus sufficiently reliable to satisfy the requirements of *Daubert* and Rule 702. Therefore, Defendants' argument that Dr. Richart's medical causation opinions should be excluded due to the lack of scientific literature cited in support of his opinions provides an insufficient basis for exclusion.

2. Defendants' Argument that Dr. Richart's Opinions Should be Excluded due to Lack of 'Absolute Certainty' Is Completely Unfounded.

Defendants argue that Dr. Richart's opinion should be excluded on the basis that he is unable to predict whether, and when, a VTE will occur at a particular point in a woman's life *with absolute certainty*. *See* Defs' Motion at 7-8. In particular, Defendants attack Dr. Richart's medical causation opinions on the grounds that he was unable to say, *with absolute certainty*, whether Plaintiff would have, or would not have, experienced a VTE while she was using

Desogen. However, such an argument is unavailing, and notably, Defendants cite no authority for such a premise.

The standard for admissibility is sufficient reliability, not absolute certainty. *Bonner*, 259 F.3d at 929. It is clear that an expert is *not* required to resolve an ultimate issue of fact to "a scientific absolute." *See Kudabeck*, 338 F.3d at 861. Neither Rule 702 nor *Daubert* requires that an expert opinion resolve an ultimate issue of fact to a scientific absolute in order to be admissible. *See Bonner*, 259 F.3d at 929. Perfect methodology is not required in order for an expert opinion to be admissible pursuant to Rule 702; Rather, the expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho*, 526 U.S. at 152.

Here, Dr. Richart's causation opinion satisfies the reliability standard. After 'ruling in' potential causes' based on extensive facts, data and pertinent medical literature, and after systematically 'ruling out' potential causes, Dr. Richart concluded that there was a causal connection between Plaintiff's NuvaRing® use and her venous thromboembolism. Further, studies support that a woman is at the greatest risk of VTE after initially starting a different hormonal contraceptive. *See e.g.,* April 2012 Yasmin Label at 6, attached hereto as Exhibit 17 ("Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC."). Because Plaintiff had been using NuvaRing® for less than two cycles at the time of her pulmonary embolism, this further supports Dr. Richart's opinion that Plaintiff was placed at an even greater risk of suffering a VTE due to her NuvaRing® use.

It is clear that Dr. Richart acted as a competent, intellectually rigorous treating physician in forming his medical causation opinion by identifying the most likely cause of Plaintiff's injury

based on a proper differential diagnosis. Therefore, Dr. Richart's opinion is sufficiently reliable under Rule 702 and the lack of "absolute certainty" provides an insufficient basis for exclusion.

V. CONCLUSION

For the foregoing reasons, Defendants' motion to exclude the testimony of Dr. John Richart must be denied.

Respectfully submitted,

Date: February 18, 2013

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CERTIFICATE OF SERVICE

I hereby certify that on February 18, 2013, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notification of such filing to all attorneys of record.

/s/ *Kristine K. Kraft*